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Field of invention

The present invention relates to new peptide-based compounds and their use in therapeutically effective treatment as well as for diagnostic imaging techniques. More specifically the invention relates to the use of such peptide-based compounds as targeting agents that bind to the heparin binding domain of vascular endothelial growth factor and its receptor vascular endothelial growth factor receptor 2 (VEGFR2/KDR(kinase insert domain-containing receptor)/flk-1 (fetal liver kinase)). VEGFR-2 is expressed on angiogenic endothelial cells, haematopoietic stem cells, endothelial precursor cells in the bone marrow, and several malignant cells. Contrast agents based on these peptides may thus be used for diagnosis of for example malignant diseases, heart diseases, endometriosis, inflammation-related diseases and rheumatoid arthritis. Moreover such agents may be used in therapeutic treatment of these diseases through inhibition of angiogenesis.

Background of invention

New blood vessels can be formed by two different mechanisms: angiogenesis or vasculogenesis. Angiogenesis is the formation of new blood vessels by sprouting/branching from existing vessels. The primary stimulus for this process may be inadequate supply of nutrients and oxygen (hypoxia) to cells in a tissue. The cells may respond by secreting angiogenic factors, of which there is many; one example, which is frequently referred to, is vascular endothelial growth factor (VEGF). These factors initiate the secretion of proteolytic enzymes that break down the proteins of the basement membrane, as well as inhibitors that limit the action of these potentially harmful enzymes. The other

prominent effect of angiogenic factors is to cause endothelial cells to migrate and divide. Endothelial cells that are attached to the basement membrane, which forms a continuous sheet around blood vessels on the contralumenal side, do not undergo mitosis. The combined effect of loss of attachment and signals from the receptors for angiogenic factors is to cause the endothelial cells to move, multiply, and rearrange themselves, and finally to synthesise a basement membrane around the new vessels. Vasculogenesis is the generation of new vessels by recruiting endothelial precursor cells from the bone marrow. Newly published data shows that vasculogenesis not only is restricted to fetal blood vessel formation, but also occurs in the adult as response to various conditions. The bone marrow derived endothelial precursor cells recruited are also expressing VEGFR2.

Angiogenesis is prominent in the growth and remodelling of tissues, including wound healing and inflammatory processes. Tumours must initiate angiogenesis when they reach millimetre size in order to keep up their rate of growth. Angiogenesis is accompanied by characteristic changes in the endothelial cells and in their environment. The surface of these cells is remodeled in preparation for migration, and cryptic structures are exposed where the basement membrane is degraded, in addition to the variety of proteins which are involved in effecting and controlling proteolysis. In the case of tumours, the resulting network of blood vessels is usually disorganised, with the formation of sharp kinks and also arteriovenous shunts. Various glycosaminoglycans (GAGs) including heparan sulfate are important players in the angiogenic interactions. Several growth factors and

their receptors including VEGF and VEGFR-2 have binding sites for heparan sulfate. Peptide mimics of GAGs may have important functions both as angiogenesis specific imaging agents, and as potential therapeutical agents through inhibition of angiogenesis.

Inhibition of angiogenesis is considered to be a promising strategy for antitumour therapy. The transformations accompanying angiogenesis are also very promising as targets for diagnosis. An obvious example is malignant disease, but the concept also shows great promise in inflammation and a variety of inflammation-related diseases, including atherosclerosis. The macrophages of early atherosclerotic lesions are potential sources of angiogenic factors. These factors are also involved in re-vascularisation of infarcts in the myocardium.

Further examples of undesired conditions that are associated with neovascularization or angiogenesis implying the development or proliferation of new blood vessels, are shown below. Reference is also made in this regard to WO 98/47541.

Diseases and indications associated with angiogenesis are e.g. different forms of cancer and metastasis, e.g. breast, skin, colorectal, pancreatic, prostate, lung or ovarian cancer.

Other diseases and indications are inflammation (e.g. chronic), atherosclerosis, rheumatoid arthritis and gingivitis.

Further diseases and indications associated with angiogenesis are arteriovenous alformations, astrocytomas, choriocarcinomas, glioblastomas, gliomas, hemangiomas (childhood, capillary), hepatomas, hyperplastic endometrium, ischemic myocardium, Kaposi sarcoma, macular degeneration, melanoma, neuroblastomas, occluding peripheral artery disease, osteoarthritis, psoriasis, retinopathy (diabetic, proliferative), scleroderma, seminomas and ulcerative colitis.

The malignant cells and the stroma cells upregulate proteins that are involved in the process of angiogenesis. More or less specific markers are expressed on the endothelial cells. These markers include growth factor receptors such as VEGFR2. Immunohistochemical studies in combination with electron microscopy have demonstrated that VEGFR2 is expressed on the abluminal and luminal plasma membranes of vascular endothelial cells (Dvorak & Feng, 2001 J Histochem Cytochem, 49:419). VEGF produced by hypoxic tumor cells or stromal cells binds to the VEGFR2 on endothelial cells and stimulate angiogenesis. As complexes of VEGF and VEGFR2 are found predominantly on the abluminal side of the vascular endothelium, VEGFR2 available for targeting by circulating ligands is available at the luminal surface.

The present invention

It has now been found a new peptide targeting the heparin binding domain of vascular endothelial growth factor and its receptor vascular endothelial growth factor receptor 2, VEGFR 2. This new peptide can be used as a therapeutic agent in a pharmaceutical formulation by inhibiting the angiogenesis in the diseased area/tissue.

Further the peptide can be coupled to a known therapeutic agent that will be carried to the diseased area/tissue by the targeting abilities of the new peptide.
One or more peptide can further be coupled to a chelating agent or a reporter moiety either by direct bonding or via a linker moiety to act as a diagnostic imaging agent or a therapeutic active agent.

Detailed description of the invention

In a first aspect, the present invention provides a new peptide that targets the heparin binding domain of VEGF and its receptor VEGFR 2..

A peptide comprising the amino acid sequence of
Z^1-$X^1X^2X^3X^4X^5GX^6X^7X^8$- Z^2
wherein
X^1 is an amino acid selected from the group Ser, His, Thr, Ala, Gln, Phe, Gly and Ile
X^2 is an amino acid selected from the group Tyr, Arg and Phe
X^3 is an amino acid selected from the group Tyr, Ser, Asn, Glu, Asp and Thr
X^4 is an amino acid selected from the group Ser, Ala, Gly, Asp and Phe
X^5 is an amino acid selected from the group Asp and Ser,
X^6 is an amino acid selected from the group Thr, Val, Met, Ser, Trp, Tyr, Leu and Ala
X^7 is an amino acid selected from the group Tyr,Phe and Leu
X^8 is an amino acid selected from the group Asp, Ser and Glu
Z^1 represent an amino acid residue capable of forming a disulphide bond, preferably a cysteine or a homocysteine residue or is absent and

Z^2 represent an amino acid residue capable of forming a disulphide bond, preferably a cysteine or a homocysteine residue or is absent
or pharmaceutically acceptable salts thereof.

More specific the new peptide comprises the amino acid sequence of

Z^1-X^1YX^3(A/S)DGX^6(Y/F)D- Z^2

wherein
X^1 is an amino acid selected from the group Ser, His, Thr, Ala, Gln, Phe; Gly and Ile
X^3 is an amino acid selected from the group Tyr, Ser, Asn, Glu, Asp and Thr
X^6 is an amino acid selected from the group Thr, Val, Met, Ser, Trp, Tyr, Leu and Ala
Z^1 represent an amino acid residue capable of forming a disulphide bond, preferably a cysteine or a homocysteine residue or is absent and
Z^2 represent an amino acid residue capable of forming a disulphide bond, preferably a cysteine or a homocysteine residue or is absent
or pharmaceutically acceptable salts thereof.

Viewed from another aspect the invention provides new peptide-based compounds as defined by formula I.

V-L-R (Formula I)

wherein the vector V is a peptide as defined above, L represents a bond, a spacer or linker and R represents an antineoplastic agent, a chelating agent or a reporter moiety.

The role of the linker L is to couple vector to reporter, and in the case where L is a spacer moiety the role of L is to distance the relatively bulky chelating agent from

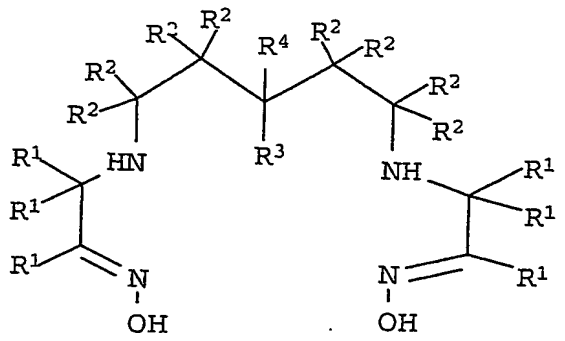
the active site of the peptide component. The spacer moiety L is also applicable to distance a bulky antineoplastic agent from the active site of the peptide.

A linker moiety may serve to link one vector to one reporter; alternatively it may link together more than one vector and/or more than one reporter. Likewise a reporter or a vector may be linked to more than one linker. Use in this way of a plurality of reporters (e.g. several linker-reporter moieties attached to one vector or several reporters attached to one linker itself attached to one vector) may enable the detectability of the contrast agent to be increased (e.g. by increasing its radioopacity, echogenicity or relaxivity) or may enable it to be detected in more than one imaging modality. Use in this way of a plurality of vectors may e.g. increase the targeting efficiency of a contrast agent or may make the contrast agent/therapeutic agent able to target more than one site, e.g. different receptors for an agent which has receptor heterogeneity.

The linker moiety L may be a simple bond or may be represented by other linkers well known in the art, e.g. as described in WO 01/77145 pages 23-27, the content of which are incorporated herein by reference.

R can be represented by stabilised gas-filled microbubbles. In this aspect of the invention the compounds of formula I can be used for targeted ultrasound imaging. Each of the microbubbles may carry several vectors V.

R can further be represented by a chelating agent of Formula II

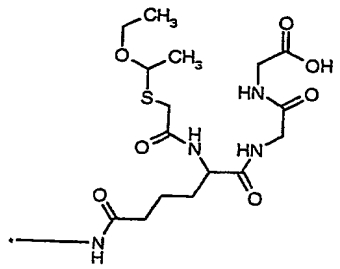


(II)

where:

each R^1, R^2, R^3 and R^4 is independently an R group;

each R group is independently H or C_{1-10} alkyl, C_{3-10} alkylaryl, C_{2-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} alkylamine, C_{1-10} fluoroalkyl, or 2 or more R groups, together with the atoms to which they are attached form a carbocyclic, heterocyclic, saturated or unsaturated ring, or can represent a chelating agent given by formulas a, b, c and d.



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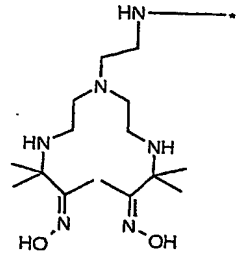

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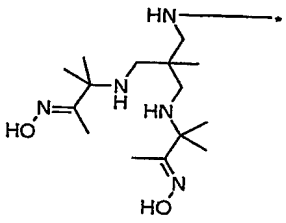

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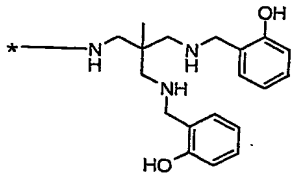
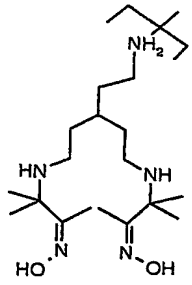


d

A preferred example of a chelating agent is represented by formula e.



e

Conjugates comprising chelating agents of Formula II can be radiolabelled to give good radiochemical purity, RCP, at room temperature, under aqueous conditions at near neutral pH. The risk of opening the disulphide bridge of the peptide component at room temperature is less than at an elevated temperature. A further advantage of radiolabelling the conjugates at room temperature is a simplified procedure in a hospital pharmacy.

However the compounds defined in Formula I may also comprise chelating agents, R, as defined in WO 01/77145, Table I, pages 11-15.

In some aspects of the invention, R comprises a reporter moiety where said reporter moiety comprises a radionuclide. Further definitions of chelating agents are listed in WO 01/77145,Table I, pages 11-15, the content of which are incorporated herein by reference.

In one aspect of the present invention of formula I R is represented by an antineoplastic agent. In this aspect the compound will target an angiogenic site associated with cancer and bring the antineoplastic agent to the diseased area.
The antineoplastic agent may be represented by cyclophosphamide, chloroambucil, busulphan, methotrexate, cytarabine, fluorouracil, vinblastine, paclitaxel, doxorubicin, daunorubicin, etoposide, teniposide, cisplatin, amsacrine, docetaxel, but a wide range of other antineoplastic agents may also be used.

The peptide component of compounds of formula I may be in a cyclic configuration, i.e. by a disulphide bond or it may be linear.
The peptide component of the conjugates described herein have preferably no free amino- or carboxy-termini. This introduces into these compounds a significant increase in resistance against enzymatic degradation and as a result they have an increased in vivo stability as compared to many known free peptides.

The reporter moieties (R) in the contrast agents of the invention may be any moiety capable of detection either

directly or indirectly in an in vivo diagnostic imaging procedure.

For MR imaging the reporter will either be a non zero nuclear spin isotope (such as ^{19}F) or a material having unpaired electron spins and hence paramagnetic, superparamagnetic, ferrimagnetic or ferromagnetic properties; for light imaging the reporter will be a light scatterer (e.g. a coloured or uncoloured particle), a light absorber or a light emitter; for magnetometric imaging the reporter will have detectable magnetic properties; for electrical impedance imaging the reporter will affect electrical impedance; and for scintigraphy, SPECT, PET, and the like, the reporter will be a radionuclide.

Stated generally, the reporter may be (1) a chelatable metal or polyatomic metal-containing ion (i.e. TcO, etc), where the metal is a high atomic number metal (e.g. atomic number greater than 37), a paramagentic species (e.g. a transition metal or lanthanide), or a radioactive isotope, (2) a covalently bound non-metal species which is an unpaired electron site (e.g. an oxygen or carbon in a persistant free radical), a high atomic number non-metal, or a radioisotope, (3) a polyatomic cluster or crystal containing high atomic number atoms, displaying cooperative magnetic behaviour (e.g. superparamagnetism, ferrimagnetism or ferromagnetism) or containing radionuclides.

Examples of particular preferred reporter groups (R) are described in more detail below.

Chelated metal reporters are preferably chosen from the group below; ^{90}Y, ^{99m}Tc, ^{111}In, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{97}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{203}Pb and ^{141}Ce.

The metal ions are desirably chelated by chelant groups on the linker moiety. Further examples of suitable chelant groups are disclosed in US-A-4647447, WO89/00557, US-A-5367080, US-A-5364613.

Methods for metallating any chelating agents present are within the level of skill in the art. Metals can be incorporated into a chelant moiety by any one of three general methods: direct incorporation, template synthesis and/or transmetallation. Direct incorporation is preferred.

Thus it is desirable that the metal ion be easily complexed to the chelating agent, for example, by merely exposing or mixing an aqueous solution of the chelating agent-containing moiety with a metal salt in an aqueous solution preferably having a pH in the range of about 4 to about 11. The salt can be any salt, but preferably the salt is a water soluble salt of the metal such as a halogen salt, and more preferably such salts are selected so as not to interfere with the binding of the metal ion with the chelating agent. The chelating agent-containing moiety is preferrably in aqueous solution at a pH of between about 5 and about 9, more preferably between pH about 6 to about 8. The chelating agent-containing moiety can be mixed with buffer salts such as citrate, carbonate, acetate, phosphate and borate to produce the optimum pH. Preferably, the buffer salts are selected so as not to interfere with the subsequent binding of the metal ion to the chelating agent.

The following isotopes or isotope pairs can be used for both imaging and therapy without having to change the radiolabeling methodology or chelator: $^{47}Sc_{21}$; $^{141}Ce_{58}$; $^{188}Re_{75}$; $^{177}Lu_{71}$; $^{199}Au_{79}$; $^{47}Sc_{21}$; $^{131}I_{53}$; $^{67}Cu_{29}$; $^{131}I_{53}$ and $^{123}I_{53}$; $^{188}Re_{75}$ and $^{99m}Tc_{43}$; $^{90}Y_{39}$ and $^{87}Y_{39}$; $^{47}Sc_{21}$ and $^{44}Sc_{21}$; $^{90}Y_{39}$ and $^{123}I_{53}$; $^{146}Sm_{62}$ and $^{153}Sm_{62}$; and $^{90}Y_{39}$ and $^{111}In_{49}$.

Preferred non-metal atomic reporters include radioisotopes such as ^{123}I, ^{131}I and ^{18}F as well as non zero nuclear spin atoms such as ^{19}F, and heavy atoms such as I.

In a further embodiment of this invention, the use of radioisotopes of iodine or fluorine is specifically contemplated. For example, if the peptide or linker is comprised of substituents that can be chemically substituted by iodine or fluorine in a covalent bond forming reaction, such as, for example, substituents containing hydroxyphenyl or p-nitrobenzoyl functionality, such substituents can be labeled by methods well known in the art with a radioisotope of iodine or fluorine respectively. These species can be used in therapeutic and diagnostic imaging applications. While, at the same time, a metal attached to a chelating agent on the same peptide-linker can also be used in either therapeutic or diagnostic imaging applications.

The compounds of formula I may be therapeutically effective in the treatment of disease states as well as detectable in in vivo imaging. Thus for example the vector on the reporter moieites may have therapeutic efficacy, e.g. by virtue of the radiotherapeutic effect of a radionuclide reporter of the vector moiety.

The present invention also provides a pharmaceutical composition comprising an effective amount (e.g. an amount effective for enhancing image contrast in in vivo imaging) of a compound of general formula I or a salt thereof, together with one or more pharmaceutically acceptable adjuvants, excipients or diluents.

The invention further provides a pharmaceutical composition for treatment of a disease comprising an effective amount of a compound of general formula I, or a salt thereof, together with one or more pharmaceutically acceptable adjuvants, excipients or diluents.

Use of the new peptide and the compounds of formula I in the manufacture of therapeutic compositions (medicament) and in methods of therapeutic or prophylactic treatment, preferably treatment of cancer, of the human or animal body are thus considered to represent further aspects of the invention.

Viewed from a further aspect the invention provides the use of a compound of formula I for the manufacture of a contrast medium for use in a method of diagnosis involving administration of said contrast medium to a human or animal body and generation of an image of at least part of said body.

Viewed from a still further aspect the invention provides a method of generating enhanced images of a human or animal body previously administered with a contrast agent composition comprising a compound as defined by formula I, which method comprises generating an image of at least part of said body.

Viewed from a further aspect the invention provides a method of monitoring the effect of treatment of a human or animal body with a drug to combat a condition associated with cancer, preferably angiogenesis, e.g. a cytotoxic agent, said method involving administering to said body an agent of formula I and detecting the uptake of said agent by cell receptors, preferably endothelial cell receptors and in particular VEGF receptors, said administration and detection optionally but preferably being effected repeatedly, e.g. before, during and after treatment with said drug.

These new compounds may be used in therapeutically effective treatments as well as for imaging purposes. Further these new compounds may be used for drug delivery purposes.

The peptides of the present invention can be synthesised using all the known methods of chemical synthesis but particularly useful is the solid-phase methodology of Merrifield employing an automated peptide synthesiser (J. Am. Chem. Soc., 85: 2149 (1964)). Typically, the desired sequences are assembled by solid-phase peptide synthesis. Standard procedures for the synthesis strategy employed for the examples of this invnetion are described in E. Atherton & R.C. Sheppard, "Solid phase peptide synthesis: a practical approach, 1989, IRL Press, Oxford. For example, a synthesis resin with an acid-labile linker group, to which the desired protected C-terminal amino acid residue has been esterified, is used. In the following examples, so-called TentaGel resins with a trityl-derived linker were applied (Bayer, E., Clausen, N., Goldammer, C., Henkel, B., Rapp, W. & Zhang, L.

(1994) in Peptides: *Chemistry, Structure and Biology* (Hodges, R.S. & Smith, J.A., eds.), pp. 156-158, ESCOM, Leiden). The amino-protected group is then removed and the second amino acid in the sequence is coupled using a suitable condensation reagent. Amino acids with semi-permanent amino protecting groups and permanent protecting groups for the functional side chains are employed. Amino-deprotection and coupling cycles are then repeated in alternating steps until the sequence of interest is assembled. Finally the permanent side-chain protecting groups are removed and the peptide is cleaved from the synthesis resin, usually simultaneously through treatment with a suitable acidic reagent.

Alternatively, the peptide can be synthesised through solution peptide synthesis methods known in the art, either in a step-wise manner from the carboxyl terminus and/or through the application of segment condensation or ligation methods, employing comprehensive or minimal protection strategies. Combined solution-solid phase segment condensation approaches can also be applied.

Generally, the reactive groups present (for example amino, hydroxyl, thiol and carboxyl groups) will be protected during overall synthesis as indicated above. The final step in the synthesis will thus be the deprotection of a protected derivative of the peptides of the invention. A wide choice of protecting groups for amino acids is known (see, e.g., Greene, T.W. & Wuts, P.G.M. (1991) Protective groups in organic synthesis, John Wiley & Sons, New York). Thus for example amino protecting groups which may be employed include 9-fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl, t-butyloxycarbonyl, etc. It will be appreciated that when

the peptide is built up from the C-terminal end, an amino-protecting group will be present on the α-amino group of each new residue added and will need to be remove selectively prior to the next coupling step. One particularly useful group for such temporary amine protection is the Fmoc group which can be removed selectively by treatment with piperidine in an organic solvent. Carboxyl protecting groups which may for example be employed include readily cleaved ester groups such as t-butyl and benzyl, as well as esters with solid phase-bound linkers, e.g. p-alkoxybenzyl, trityl, etc. It will be appreciated that a wide range of other such groups are known in the art.

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<211> 11
<212> PRT
<213> Artificial sequence
<220>
<223> Syntetic peptide
<400> 14

Cys Ser Tyr Tyr Ala Asp Gly Met Tyr Ser Cys
1 5 10

Claims

1. A peptide comprising the amino acid sequence of
Z^1-$X^1X^2X^3X^4X^5GX^6X^7X^8$- Z^2
wherein
X^1 is an amino acid selected from the group Ser, His, Thr, Ala, Gln, Phe, Gly and Ile
X^2 is an amino acid selected from the group Tyr, Arg and Phe
X^3 is an amino acid selected from the group Tyr, Ser, Asn, Glu, Asp and Thr
X^4 is an amino acid selected from the group Ser, Ala, Gly, Asp and Phe
X^5 is an amino acid selected from the group Asp and Ser,
X^6 is an amino acid selected from the group Thr, Val, Met, Ser, Trp, Tyr, Leu and Ala
X^7 is an amino acid selected from the group Tyr, Phe and Leu
X^8 is an amino acid selected from the group Asp, Ser and Glu
Z^1 represent an amino acid residue capable of forming a disulphide bond, preferably a cysteine or a homocysteine residue or is absent and
Z^2 represent an amino acid residue capable of forming a disulphide bond, preferably a cysteine or a homocysteine residue or is absent
or pharmaceutically acceptable salts thereof.

2. A peptide according to claim 1 comprising the amino acid sequence of
Z^1-X^1YX^3(A/S)DGX^6(Y/F)D- Z^2
wherein
X^1 is an amino acid selected from the group Ser, His,

Thr, Ala, Gln, Phe, Gly and Ile
X^3 is an amino acid selected from the group Tyr, Ser, Asn, Glu, Asp and Thr
X^6 is an amino acid selected from the group Thr, Val, Met, Ser, Trp, Tyr, Leu and Ala
Z^1 represent an amino acid residue capable of forming a disulphide bond, preferably a cysteine or a homocysteine residue or is absent and
Z^2 represent an amino acid residue capable of forming a disulphide bond, preferably a cysteine or a homocysteine residue or is absent
or pharmaceutically acceptable salts thereof.

3. A peptide according to claim 1 of the amino acid sequence C-SYYSDGVYD-C, (SEQ ID NO 1).

4. A peptide according to claim 1 of the amino acid sequence C-HYSSDGTYD-C, (SEQ ID NO 2).

5. A peptide according to claim 1 of the amino acid sequence C-TYNGDGSFD-C, (SEQ ID NO 3).

6. A peptide according to claim 1 of the amino acid sequence C-AYEADGWFD-C, (SEQ ID NO 4).

7. A peptide according to claim 1 of the amino acid sequence C-SYSADGTLD-C, (SEQ ID NO 5).

8. A peptide according to claim 1 of the amino acid sequence C-QYDSSGMYD-C, (SEQ ID NO 6).

9. A peptide according to claim 1 of the amino acid sequence C-FFDSSGYFD-C, (SEQ ID NO 7).

10. A peptide according to claim 1 of the amino acid sequence C-TYSADGLYD-C, (SEQ ID NO 8).

11. A peptide according to claim 1 of the amino acid sequence C-HFDGDGSYD-C, (SEQ ID NO 9).

12. A peptide according to claim 1 of the amino acid sequence C-TYEPSGMYD-C, (SEQ ID NO 10).

13. A peptide according to claim 1 of the amino acid sequence C-QYTADGAFD-C, (SEQ ID NO 11).

14. A peptide according to claim 1 of the amino acid sequence C-IYESDGMFS-C, (SEQ ID NO 12).

15. A peptide according to claim 1 of the amino acid sequence C-GRSDGTWYE-C, (SEQ ID NO 13).

16. A peptide according to claim 1 of the amino acid sequence C-SYYADGMYS-C, (SEQ ID NO 14).

17. A targetable diagnostic and/ or therapeutically active agent of formula I

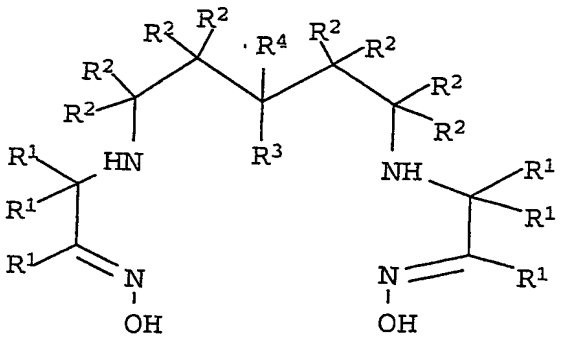
V-L-R (Formula I)

wherein the vector V is a peptide according to claim 1- 16

L represents a bond, a spacer or a linker and

R represents an antineoplastic agent a chelating agent or a reporter moiety.

18. An agent as claimed in claim 17 where R is a chelating agent of Formula II



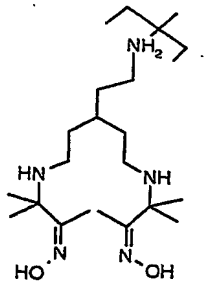
(II)

where:

each R^1, R^2, R^3 and R^4 is independently an R group;

each R group is independently H or C_{1-10} alkyl, C_{3-10} alkylaryl, C_{2-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} alkylamine, C_{1-10} fluoroalkyl, or 2 or more R groups, together with the atoms to which they are attached form a carbocyclic, heterocyclic, saturated or unsaturated ring.

19. An agent as claimed in claims 17 and 18 where R is



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20. An agent as claimed in any of the previous claims 17 to 19 wherein R comprises a reporter moiety.

21. An agent as claimed in claim 20 wherein the reporter moiety comprises metal radionuclides, paramagnetic metal ions, fluorescent metal ions, heavy metal ions or cluster ions.

22. An agent as claimed in claims 20 and 21 wherein the reporter moiety comprises ^{90}Y, ^{99m}Tc, ^{111}In, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{97}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{203}Pb, ^{141}Ce or ^{18}F.

23. An agent as claimed in claims 17-22 wherein the reporter moiety is ^{99m}Tc.

24. An agent as claimed in claim 17 where R represent stabilised gas-filled microbubbles.

25. An agent as claimed in claims 17 to 24 where each reporter (R) can carry a multiplicity of vectors V.

26. An agent as claimed in claim 17 where R is an antineoplastic agent.

27. An agent as claimed in claim 26 where R represent cyclophosphamide, chloroambucil, busulphan, methotrexate, cytarabine, fluorouracil, vinblastine, paclitaxel, doxorubicin, daunorubicin, etoposide, teniposide, cisplatin, amsacrine or docetaxel.

28. A pharmaceutical composition comprising an effective amount of a compound of general Formula (I) or a salt thereof, together with one or more pharmaceutically acceptable adjuvants, excipients or diluents for use in enhancing image contrast in *in vivo* imaging or for treatment of a disease.

29. Use of a compound as claimed in any one of claims 17 to 25 in the preparation of a contrast medium for use in a method of diagnosis involving administering said contrast medium to a human or animal body and generating an image of at least part of said body.

30. A method of generating images of a human or animal body involving administering a contrast agent to said body, and generating an image of at least a part of said body to which said contrast agent has distributed, characterised in that said contrast agent comprises a compound as claimed in any one of claims 17 to 25.

31. A method of generating enhanced images of a human or animal body previously administered with a contrast agent composition comprising a compound as claimed in claims 17 to 25, which method comprises generating an image of at least part of said body.

32. A method of monitoring the effect of treatment of a human or animal body with a drug to combat a condition associated with cancer, said method involving administering to said body a compound or composition as claimed in any one of claims 17 to 25 and detecting the uptake of said compound or composition by cell receptors, said administration and detection optionally but preferably being effected repeatedly, e.g. before, during and after treatment with said compound or composition.

33. A method of treating cancer or a related disease in a human or animal body which comprises the administration of an effective amount of a compound or composition as claimed in any one of claims 1 to 27

34. Use of a compound as claimed in any one of claims 1 to 16 for the manufacture of a medicament for the therapeutic or prophylactic treatment of cancer or a related disease in a human or animal.

35. Use of a compound as claimed in any one of claims 1 to 16 for the manufacture of a medicament for the therapeutic or prophylactic treatment of or a related disease in a human or animal.

Abstract

The present invention relates to a new peptide for targeting that bind to the heparin binding domain of vascular endothelial growth factor and its receptor vascular endothelial growth factor receptor 2, VEGFR-2. The invention further relates to their use in therapeutically effective treatment as well as for diagnostic imaging techniques.